REMARKS

Claims 1-42 were pending in the instant application. Claims 15-42 have been cancelled without prejudice. Claims 1, 8 and 11-14 have been amended, and claim 43 has been added. Accordingly, claims 1-14 and 43 will be pending in the application upon entry of the claim amendments presented herein. In addition, amendments to the specification have been made at the following locations: page 20, line 21; page 20, line 22; page 37, line 18; page 38, line 8; page 39, line 11; page 39, line 16; page 40, line 23; page 62, line 40; page 62, line 41; page 63, line 38; page 63, line 39; page 63, line 40; page 63, line 48; page 63, line 49; page 63, line 50; page 63, line 51; page 63, line 52; page 63, line 53; page 64, line 5; page 64, line 6; page 64, line 10; page 64, line 11; page 64, line 17; page 64, line 18; page 64, line 19; page 64, line 20; page 64, line 21; page 64, line 22; page 64, line 23; page 64, line 24; page 64, line 36; page 64, line 37; page 64, line 38; page 64, line 39; page 64, line 40; page 64, line 41; page 64, line 42; page 64, line 43; page 67, line 18; page 67, line 19; page 67, line 24; page 67, line 26; page 67, lines 29 and 30; page 67, line 31, page 67, line 43; and page 67, line 44.

Claims 1, 8 and 11-14 have been amended to make editorial changes. Claim 14 has been amended to insert a sequence identifier inadvertently left out of the application as originally filed. Support for the claim amendments can be found throughout the specification and claims as originally filed. In particular, support for the amendments to claim 1 can be found at least, for example, in the specification at page 7, lines 5-34. Support for new claim 43 can be found in the specification at least at page 4 lines 13-15. No new matter has been added.

Cancellation of and amendment to the claims as originally filed should in no way be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, and were made solely to expedite prosecution of the above-identified application. Applicants reserve the option to prosecute the same or similar claims in the instant application or in one or more or subsequent applications.

For the convenience of the Examiner, the claims that will be pending upon entry of the claim amendments presented herein are attached hereto as Appendix A1.

Election/ Restrictions

Applicants note that the restriction requirement was made final with the election of Group I, claims 1-14. Accordingly, claims 15-42 have been cancelled without prejudice as directed to non-elected subject matter. Nevertheless, Applicants reserve the option to pursue the non-elected subject matter of cancelled claims 15-42 in one or more divisional applications.

Specification

The Examiner has kindly pointed out that the disclosure does not identify sequences by SEQ ID NO's. Applicants have corrected this informality by amending the specification to add the sequence identifiers which were inadvertently left out of the application as originally filed.

Formal Matters

The Examiner has kindly pointed out that square brackets were used by Applicants in claims 1 and 14, and that square brackets are to be used only to designate text to be deleted in amendments. Therefore, claims 1 and 14 have been amended to replace the square brackets with parentheses.

Claim Rejections - 35 U.S.C. §112, First Paragraph

Rejection of Claims 1-14 under 35 U.S.C. §112, First Paragraph

Claims 1-14 are rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Office Action, at pages 4 and 5, states that "[c]laim 1 defines a G protein coupled receptor by a function alone, *i.e.* that upon interaction with a ligand to modulate a signal transduction pathway in a cell, a signal generated by said mutant receptor is greater than a signal generated upon interaction of said ligand with a wild type G protein-coupled receptor."

The Office Action further asserts that "[w]hile Applicant has set forth the desired functions of a mutant mammalian G protein coupled receptor, Applicant has not set forth within the claim the detailed constitution of the mutant mammalian G protein coupled receptor, and thus does not satisfy the written description requirement." Applicants respectfully traverse this rejection.

Applicants respectfully submit that originally filed claim 1, and the claims depending therefrom, not only recite a description of the function of the mutant G protein coupled receptor, but also a description of the structure of the mutant G protein coupled receptor. These same descriptions also appear in the specification as originally filed.

With regard to the structural description of the receptor, the Examiner's attention is invited to claim 1 which recites a mutant G protein coupled receptor containing the ***specific amino acid sequence motif, ($X_1X_2X_3X_4$) proximal to the carboxy terminal end of the wild type amino acid sequence***, where X_1 denotes an amino acid residue at position 1 of said motif and is selected from the group consisting of Phe, Leu, Val, and Tyr; X_2 denotes an amino acid residue at position 2 of said motif and is selected from the group consisting of Phe, Lys and Gln; X_3 denotes an amino acid residue at position 3 of said motif and is selected from the group consisting of Leu, Arg, Glu, Asn, Gln, Ser, Ala, Leu ; and X_4 denotes an amino acid residue at position 4 of said motif and is selected from the group consisting of Ala, Cys, Asp, Glu, Gly, Ser, Thr and Tyr. The claim further recites that the mutant receptor ***comprises a seventh transmembrane with a carboxy terminal end***, and ***at least one point mutation*** at a position ***in the ($X_1X_2X_3X_4$) amino acid motif***; ***such that*** upon interaction with a ligand, said mutant receptor is capable of modulating a signal transduction pathway in a cell, wherein ***a signal generated by said mutant receptor is greater than a signal generated*** upon interaction of said ligand ***with a wild type G protein-coupled receptor***.

Clearly, claim 1, and for example, page 7, lines 17-34, of the instant specification, describe at least three significant structural features of the claimed mutant G protein coupled receptors, as well as the function of the receptor that results from the receptor possessing these structural features. In addition, the claim and corresponding sections of

the specification provide the wild type amino acid sequence as a frame of reference for the structure of the mutant receptor. The specification (for example, at page 7, lines 10-11 and Examples 2 and 3) also provides two specific examples of mutant mammalian IL-8 and galanin receptors.

Therefore, the statement in the Office Action at page 4, item section 5(a), that claim 1 defines the recited G protein coupled receptor by a function alone is inaccurate. Furthermore, Applicants assert that the disclosure of the aforementioned structural features and the function of the G protein receptor, as well as of specific examples of mutant receptors in accordance with the invention, is sufficient to meet the written description requirement of the first paragraph of 35 U.S.C. §112. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-14 under 35 U.S.C. §112, First Paragraph

Claims 1-14 are rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a mutant IL8 receptor and a mutant galanin receptor, does not reasonably provide enablement for any other mutant mammalian G protein coupled receptor." The Office Action, at pages 5 and 6, asserts that "[c]laim 1 is overly broad in the recitation of "mutant mammalian G protein coupled receptor", since no guidance as to what constitutes "mutant mammalian G protein coupled receptor" is provided within the claims. The broad scope of claim 1 can be read to encompass any isolated mutant mammalian G protein coupled receptor. There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a mutant mammalian G protein coupled receptor other than those exemplified in the specification." The Office Action further states that "[g]iven the breadth of claims 1-14 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. Claims 2-14 are rejected insofar as they depend on the recitation in claim 1 of "mutant mammalian G protein coupled receptor."

Applicants respectfully traverse this rejection.

G protein coupled receptors (GPCRs) have been extensively studied and were well known and thoroughly described in the art at the time the application was filed. Many GPCRs have been identified and the structural and functional properties of various GPCRs are known. In fact, nearly 2000 GPCRs have been reported.

GPCRs are described as containing seven transmembrane domains, having the ability to bind G proteins, and transducing signals within a cell. In addition to containing seven transmembrane domains, GPCRs are all known to contain an extracellular N-terminal segment, three exoplasmic loops, three cytoplasmic loops, and a C-terminal segment (Ji *et al.* (1998) *J. Biol. Chem.* 273:17299-17302, set forth in Appendix A2). GPCRs are also thought to share a common method of receptor activation wherein ligand binding causes receptor activation leading to changes in the relative orientations of transmembrane helices 3 and 6, which then changes the conformation of G protein-interacting intracellular loops of the GPCR, uncovering previously masked G-protein-binding sites (Hamm (1998) *J. Biol. Chem.* 273:669-672, set forth in Appendix A3). The instant specification, at least at pages 1-6, describes the common physical characteristics and activities which constitute GPCRs.

Inasmuch as GPCRs have been well studied, the level of skill in the art is very high. Furthermore, given the high level of skill in the art and Applicants' teachings as discussed below in more detail, there is a high level of predictability in practicing Applicants' invention.

Claim 1 is drawn to a GPCR that 1) contains the motif $X_1X_2X_3X_4$ and 2) contains at least one point mutation in the motif $X_1X_2X_3X_4$ which gives the protein greater signaling ability than is observed in the wild type protein. Applicants' examples (specification pages 62-67, discussed in more detail below) teach a specific mutation in the $X_1X_2X_3X_4$ motif in both the IL-8 receptor as well as the GalR1 which causes increased GPCR signaling. The nature of the invention is, therefore, clearly taught by Applicants.

In the specification, Applicants set forth detailed methods for making mutant G protein coupled receptors (GPCRs) of the invention. Applicants teach a specific amino acid motif wherein one or more point mutations are introduced in order to make the GPCRs of the invention (see, for example, page 7, lines 17-34). Furthermore, Applicants teach several methods to generate point mutations such as site directed mutagenesis as well as random mutagenesis (page 29, line 38 to page 31 line 21). Applicants teach suitable host cells (page 24 lines 13-29), expression systems (page 24, line 31 to page 26, line 11), and methods of expressing heterologous receptors in host cells (page 26 line 13 to page 27, line 40). Applicants teach methods of screening for mutant GPCRs which have increased signaling. At page 23 lines 29-42, Applicants teach a screening assay whereby yeast cells expressing a heterologous GPCR are contacted with a test compound wherein changes in signaling mediated by a mutated GPCR relative to a wild type receptor identify the compound as a modulator of the GPCR. Examples of suitable test compounds are numerous and include peptides, nucleic acids, carbohydrates, small organic molecules, and natural product extract libraries. Examples of detectable signals which may be used are taught by Applicants and include signals such as cellular second messengers and reporter constructs which are described at least at page 52, line 33 to page 61, line 19.

Applicants also provide working examples that teach how to make and express GPCRs of the invention. Example 1 teaches the expression of the IL-8A receptor in both yeast and mammalian cells (specification page 62, line 33 to page 63, line 20). Example 2 demonstrates the co-expression of the IL-8 receptor and ligands of the IL-8A receptor in the same cell (page 63, line 23 to page 64, line 43). Example 2 (page 64, line 47 to page 67, line 7) details the creation of a mutant IL-8A receptor as well as methods of selecting for desired mutant proteins. This example further teaches how to use a β-galactosidase reporter assay as well as assaying cellular second messenger concentration in order to quantitate mutant GPCR signaling. Example 3 teaches generating a mutant galanin receptor-1 (GalR1) based upon a mutation that was shown to increase IL-8A receptor signaling in the previous examples (page 67, lines 10 to 58). The mutation

which increased the IL-8A receptor response to ligand similarly caused an increased response to ligand in the GalR1 as well. These examples, therefore, establish a ***correlation*** between the ***function of GPCRs*** and ***specific amino acids within the $X_1X_2X_3X_4$ motif***.

In summary, Applicants teach a specific GPCR motif to be mutated in order to increase signaling, as well as assays to screen for such mutant proteins. Methods of mutagenesis are taught in the specification and are well known to those of skill in the art. Furthermore, methods of screening large numbers of yeast colonies are routine to those of skill in the art. Therefore, practicing Applicants' invention would not present undue experimentation to one of skill in the art.

Given the large number of GPCRs known in the art, the known physical and functional properties of GPCRs, the high level of skill in the art of GPCRs, Applicants' disclosure of specific mutations to be made within GPCRs leading to increased signaling, the disclosed correlation between the structure of the $X_1X_2X_3X_4$ motif and the signaling function of GPCRs, Applicants' teachings in the specification for making the GPCRs that are claimed, Applicants' teachings of working examples, the low level of experimentation necessary to practice Applicants' invention, and the admission by the Office Action that the specification is "enabling for a mutant IL8 receptor and a mutant galanin receptor", it would be routine for one of ordinary skill in the art to generate a mutant GPCR containing a mutation in the $X_1X_2X_3X_4$ motif which causes increased signaling when compared to the wild type GPCR. Accordingly, Applicants assert that the full scope of the claims as presented herein is enabled by the disclosure of the instant application, and Applicants respectfully request reconsideration and withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 U.S.C. §112, Second Paragraph

Rejection of Claims 1-14 under 35 U.S.C. §112, Second Paragraph

Claims 1-14 are rejected under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention." The Office Action asserts that there is insufficient antecedent basis for the limitation "said domain" in claim 1; the term "varies" is not defined by claim 1, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention; the term "near" is not defined by claim 1, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention; and the phrase "such that" renders the claim indefinite.

Applicants respectfully traverse this rejection. However, without acquiescing to the rejection, and in the interests of expediting prosecution, claim 1 has been amended. Applicants submit that the rejections based upon the terms "said domain", "varies", "near", and "such that" do not apply to claim 1, as presented herein, and the claims depending from claim 1.

Moreover, the Office Action alleges that "[c]laim 1 is drawn to a mutant G protein coupled receptor, not a cell", so there is insufficient antecedent basis for the limitation "said cell" in claims 2-5. Applicants respectfully disagree.

Applicants respectfully invite the Examiner's attention to claim 1, as originally filed, which is set forth in the application on page 69, lines 23 and 24. The claim recites "a signal transduction pathway in a ***cell***" (bold and italics added for emphasis). Claim 1 therefore provides sufficient antecedent basis for the limitation "said cell" in claims 2-5. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The Office Action further alleges that claims 8 and 13 are indefinite in that there is nothing in these claims which "distinctly claims the protein and variants thereof", and that the receptors should be distinctly claimed by "claiming structural characteristics associated with the protein." Applicants respectfully traverse this rejection.

However, without acquiescing to the rejection, and in the interests of expediting prosecution, claims 8 and 13 have been amended. Specifically, claim 8 now recites that the wild type G protein coupled receptor is the IL8A receptor. Similarly, claim 13 now recites that the wild type G protein coupled receptor is the human galanin-1 receptor.

IL-8 receptors are described in the specification and are well known in the art (specification, page 3, line 7 to page 6, line 28; and page 20, line 28 to page 21, line 15). Both physical and functional characteristics of IL-8A receptors were known in the art at the time the application was filed. Specifically, IL-8 receptors are members of the rhodopsin family, have a seven transmembrane spanning region, transduce phosphoinositol hydrolysis, capable of rapid elevations of diacylglycerol and cytosolic Ca^{2+} levels, and are expressed by neutrophils.

Galanin receptors are also described in the specification and are well known in the art (specification page 21, lines 18-36). Both physical and functional characteristics of galanin receptors were known in the art at the time the application was filed. Specifically, members of the galanin receptor family are glycoproteins which have seven transmembrane domains and bind the neuropeptide galanin (Habert-Ortoli *et al.* (1994) *J. Biol. Chem.* 91:9780-9783; Wang *et al.* (1997) *J. Biol. Chem.* 272:31949-31952, set forth in Appendices D and E, respectively).

When claims 8 and 13 as presented herein are read in light of the specification, in particular the excerpts noted above, Applicants assert that the claims would be sufficiently definite to one of ordinary skill in the art. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-14 under 35 U.S.C. § 112, second paragraph.

Claim Rejections - 35 U.S.C. §102 (b)

Rejection of Claims 1, 5, 8, and 10-11 under 35 U.S.C. §102 (b)

Claims 1, 5, 8, and 10-11 are rejected under 35 U.S.C. § 102 (b), "as being anticipated by Navarro *et al.* (WO 92/18641)." In particular, the Office Action, at page 8, states that

> "Navarro *et al.* discloses a mammalian IL8 receptor (page 10, lines 5-14). This receptor comprises a LFGA motif near the carboxy terminal (Figure 1, drawing Sheet 2, third line; Sequence Comparison A), and a seventh transmembrane domain. Navarro *et al.* discloses that specific receptor analogs include full-length or partial receptor proteins including an amino acid sequence which

> differs only by conservative amino acid substitutions, for example, substitution of one amino acid for another of the same class, or by one or more non-conservative amino acid substitutions, deletions, or insertions (page 10, line 32 to page 11, line 7) . Thus claims 1, 8 and 11 are anticipated."

Applicants respectfully traverse the foregoing rejection of claim 1, and the claims depending therefrom, for the following reasons.

For a reference to anticipate a claimed invention under 35 U.S.C. 102, the reference must teach ***each and every element*** of the claimed invention. See M.P.E.P. 2143. As amended, claim 1 is directed to a ***mutant*** mammalian G-protein coupled receptor having an amino acid sequence which ***differs from a wild type*** G protein-coupled receptor ***having a wild type amino acid sequence*** comprising the amino acid motif ($X_1X_2X_3X_4$) proximal to the carboxy terminal end of said wild type amino acid sequence, which contains ***at least one point mutation at a position in said amino acid motif***; such that upon interaction with a ligand, said mutant receptor is capable of modulating a signal transduction pathway in a cell, wherein ***a signal generated*** by said mutant receptor ***is greater than a signal generated*** upon interaction of said ligand with ***a wild type G protein-coupled receptor***.

Navarro *et al.* teach an amino acid sequence (SEQ ID NO:1; Figure 1) of a receptor which is ***identical*** to the ***wild-type rabbit sequence*** (see Pub Med Accession # P21109, set forth in Appendix A4). Thus, SEQ ID NO:1 is not a mutant of the wild type sequence. The Navarro *et al.* reference contains a mere passing reference to an amino acid substitution and gives no specific disclosure of a mutation within the $X_1X_2X_3X_4$ motif. Navarro *et al.* ***do not specifically teach*** mutating amino acids within the $X_1X_2X_3X_4$ motif, resulting in a mutation of one of the following amino acids: X_1 denotes Phe, Leu, Val, and/or Tyr; X_2 denotes Phe, Lys and/or Gln; X_3 denotes Leu, Arg, Glu, Asn, Gln, Ser, Ala, and/or Leu; and X_4 denotes Ala, Cys, Asp, Glu, Gly, Ser, Thr and/or Tyr. More importantly, Navarro *et al.* neither teach nor suggest a substitution in this sequence that would cause a signal to be generated upon ligand binding that is ***greater*** than a signal generated by the wild-type receptor. Accordingly, as Navarro *et al.* fail to

teach ***each and every element*** of claim 1 and claims depending therefrom, Applicants respectfully request that this section 102(b) rejection be reconsidered and withdrawn.

Rejection of Claims 1-2, 4-5, and 11-12 under 35 U.S.C. §102 (b)

Claims 1-2, 4-5, and 11-12 are rejected under 35 U.S.C. § 102 (b), "as being anticipated by Bergsman *et al.* (WO 96/18651)." In particular, the Office Action, at page 9, states that

> "Bergsman *et al.* discloses a human somatostatin receptor (page 3, line 23). The receptor comprises a PPLA motif proximal to the carboxy terminal (page21, third line; Sequence Comparison B), and a seventh transmembrane domain. Bergsman *et al.* discloses that mutants of the receptor may be prepared by the deletion of a portion of the sequence encoding the protein, by insertion of a sequence, and/or by substitution of one or more nucleotides within the sequence. The receptor disclosed in Bergsman *et al.* is expressed in human host cell lines (page 16, line 5), and yeast expression vectors are also envisaged (page 8, line 11) thus claims 1-2, 4-5 and 11-12 are anticipated."

Applicants respectfully traverse the foregoing rejection of claim 1 and claims depending therefrom for the following reasons. For a reference to anticipate a claimed invention under 35 U.S.C. 102, the reference must teach ***each and every element*** of the claimed invention. See M.P.E.P. 2143.

As amended, claim 1 is directed to a ***mutant*** mammalian G-protein coupled receptor having an amino acid sequence which ***differs from a wild type*** G protein-coupled receptor ***having a wild type amino acid sequence*** comprising the amino acid motif ($X_1X_2X_3X_4$) proximal to the carboxy terminal end of said wild type amino acid sequence, which contains ***at least one point mutation at a position in said amino acid motif***; such that upon interaction with a ligand, said mutant receptor is capable of modulating a signal transduction pathway in a cell, wherein ***a signal generated*** by said mutant receptor ***is greater than a signal generated*** upon interaction of said ligand with ***a wild type G protein-coupled receptor***.

Bergsman *et al.* teach an isolated human somatostatin-like receptor (SEQ ID NO:2) containing the wild-type sequence of the receptor (see Pub Med Accession #

AAC14587, set forth in Appendix A5). Thus, SEQ ID NO:2 is not a mutant of the wild type sequence. The Bergsman *et al.* reference contains a mere passing reference to an amino acid substitution and gives no specific disclosure of a mutation within the $X_1X_2X_3X_4$ motif. Bergsman *et al.* ***do not specifically teach*** mutating amino acids within the $X_1X_2X_3X_4$ motif, resulting in a mutation of one of the following amino acids: X_1 denotes Phe, Leu, Val, and/or Tyr; X_2 denotes Phe, Lys and/or Gln; X_3 denotes Leu, Arg, Glu, Asn, Gln, Ser, Ala, and/or Leu; and X_4 denotes Ala, Cys, Asp, Glu, Gly, Ser, Thr and/or Tyr. More importantly, Bergsman *et al.* neither teach nor suggest a substitution in this sequence that would cause a signal to be generated upon ligand binding that is ***greater*** than a signal generated by the wild-type receptor. Accordingly, as Bergsman *et al.* fail to teach ***each and every element*** of claim 1 and claims depending therefrom, Applicants respectfully request that this section 102(b) rejection be reconsidered and withdrawn.

Rejection of Claims 1, 5, and 11-13 under 35 U.S.C. §102 (b)

Claims 1, 5, and 11-13 are rejected under 35 U.S.C. § 102 (b), "as being anticipated by Hinuma *et al.* (EP 0711830A2)." In particular, the Office Action, at pages 9 and 10, states that

> "Hinuma *et al.* discloses a human galanin receptor (page 4, line 58 to page 5, line 8). The receptor comprises an FLSE motif near the carboxy terminal (page 58, amino acids 305-309), and a seventh transmembrane domain. Hinuma *et al.* discloses that the galanin receptor protein can be modified by, *e.g.*, addition, deletion, substitution with other amino acids, etc (page 15, lines 49-50). The receptor disclosed in Hinuma *et al.* is expressed in 293 cells (page 18, lines 49-56). Thus, claims 1, 5 and 11-13 are anticipated."

Applicants respectfully traverse the foregoing rejection of claim 1 and claims depending therefrom for the following reasons. For a reference to anticipate a claimed invention under 35 U.S.C. 102, the reference must teach ***each and every element*** of the claimed invention. See M.P.E.P. 2143.

As amended, claim 1 is directed to a ***mutant*** mammalian G-protein coupled receptor having an amino acid sequence which ***differs from a wild type*** G protein-coupled receptor ***having a wild type amino acid sequence*** comprising the amino acid motif ($X_1X_2X_3X_4$) proximal to the carboxy terminal end of said wild type amino acid sequence, which contains ***at least one point mutation at a position in said amino acid motif***; such that upon interaction with a ligand, said mutant receptor is capable of modulating a signal transduction pathway in a cell, wherein ***a signal generated*** by said mutant receptor ***is greater than a signal generated*** upon interaction of said ligand with ***a wild type G protein-coupled receptor***.

Hinuma *et al.* teach an isolated human galanin receptor (Figure 6) containing the wild-type sequence of the receptor (see Pub Med Accession # P25024, set forth in Appendix A6). Thus, the isolated human galanin receptor is not a mutant of the wild type sequence. The Hinuma *et al.* reference contains a mere passing reference to an amino acid substitution and gives no specific disclosure of a mutation within the $X_1X_2X_3X_4$ motif. Hinuma *et al.* ***do not specifically teach*** mutating amino acids within the $X_1X_2X_3X_4$ motif, resulting in a mutation of one of the following amino acids: X_1 denotes Phe, Leu, Val, and/or Tyr; X_2 denotes Phe, Lys and/or Gln; X_3 denotes Leu, Arg, Glu, Asn, Gln, Ser, Ala, and/or Leu; and X_4 denotes Ala, Cys, Asp, Glu, Gly, Ser, Thr and/or Tyr. More importantly, Hinuma *et al.* neither teach nor suggest a substitution in this sequence that would cause a signal to be generated upon ligand binding that is ***greater*** than a signal generated by the wild-type receptor. Accordingly, as Hinuma *et al.* fail to teach ***each and every element*** of claim 1 and claims depending therefrom, Applicants respectfully request that this section 102(b) rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, entry into the record of this application of the foregoing amendments and remarks, reconsideration and withdrawal of all the rejections, and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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APPENDIX A1

1. (Amended) A mutant mammalian G-protein coupled receptor having an amino acid sequence which [varies] differs from a wild type G protein-coupled receptor having a wild type amino acid sequence comprising an amino acid motif [[$X_1X_2X_3X_4$]] ($X_1X_2X_3X_4$) [lying near] proximal to the carboxy terminal end of said [domain] wild type amino acid sequence, wherein:

X_1 denotes an amino acid residue at position 1 of said motif and is selected from the group consisting of Phe, Leu, Val, and Tyr;

X_2 denotes an amino acid residue at position 2 of said motif and is selected from the group consisting of Phe, Lys and Gln;

X_3 denotes an amino acid residue at position 3 of said motif and is selected from the group consisting of Leu, Arg, Glu, Asn, Gln, Ser, Ala, Leu ; and

X_4 denotes an amino acid residue at position 4 of said motif and is selected from the group consisting of Ala, Cys, Asp, Glu, Gly, Ser, Thr and Tyr; and

wherein said mutant receptor comprises a seventh transmembrane domain with a carboxy terminal end;

at least one point mutation at a position in said amino acid motif;

[such that] wherein upon interaction with a ligand to modulate a signal transduction pathway in a cell, a signal generated by said mutant receptor is greater than a signal generated upon interaction of said ligand with a wild type G protein-coupled receptor.

2. The receptor of claim 1, wherein said cell is a yeast cell.

3. The receptor of claim 2, wherein said receptor acts as a surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of said cell.

4. The receptor of claim 2, wherein said cell belongs to the species *Saccharomyces cerevisiae*.

5. The receptor of claim 1, wherein said cell is a mammalian cell.

6. The receptor of claim 1, wherein said receptor containing said amino acid motif with no point mutation thereon generates no detectable signal.

7. The receptor of claim 1, wherein said point mutation comprises mutagenization at position 4 of said amino acid motif to Arg or to Lys.

8. (Amended) The receptor of claim 1, [comprising an] wherein said wild type G protein coupled receptor is IL8A receptor.

9. The receptor of claim 8, wherein said point mutation is selected from the group consisting of : Arg to Trp at position 73, Met to Ile at position 246; and Gly to Arg at position 320.

10. The receptor of claim 8, wherein said ligand is interleukin 8 (IL8) or melanoma growth-stimulating activity-alpha (MGSA/GROα).

11. (Amended) The receptor of claim 1 [comprising], wherein said wild type G protein coupled receptor is a human receptor.

12. (Amended) The receptor of claim 11 , wherein said wild type G protein coupled receptor is selected from the group consisting of human galanin-1 receptor, somatastatin receptor type I, somatastatin receptor type II, somatastatin receptor type III, and human nociceptin receptor.

13. (Amended) The receptor of claim 12, [which] wherein said wild type G protein coupled receptor is human galanin-1 receptor.

14. (Amended) The receptor of claim 13, comprising an amino acid sequence LAYSNSSVNPIIYAFLSEN**[**[FRK**R**]**]** (FRK**R**)YKQV (SEQ ID NO:1) wherein said mutant amino acid motif within said sequence is **[**[FRK**R**]**]** (FRK**R**).

43. (New) The receptor of claim 1, wherein said wild type G protein coupled receptor is a member of the rhodopsin family of receptors.